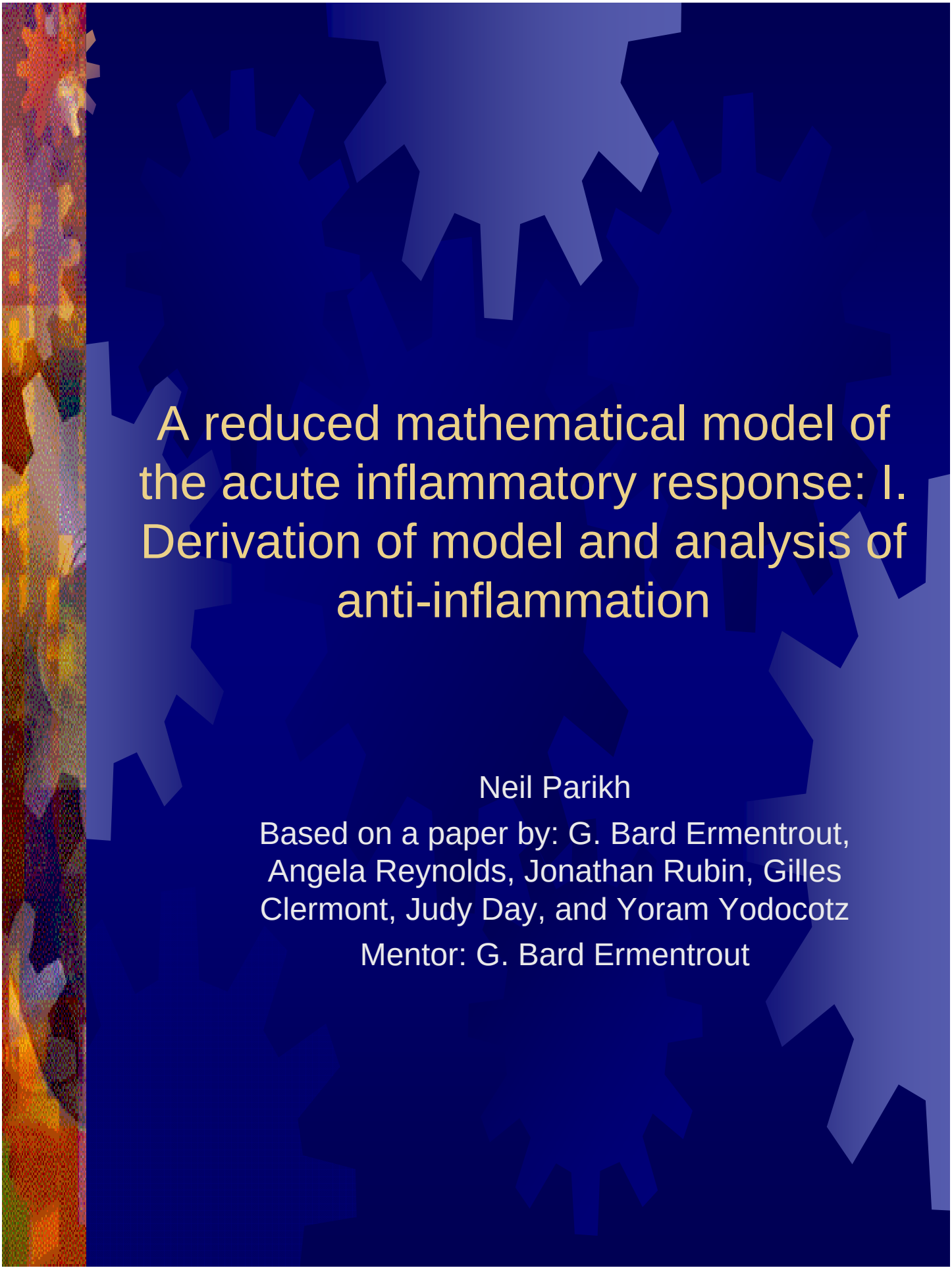


A reduced mathematical model of the acute inflammatory response: I. Derivation of model and analysis of anti-inflammation

Neil Parikh

Based on a paper by: G. Bard Ermentrout, Angela Reynolds, Jonathan Rubin, Gilles Clermont, Judy Day, and Yoram Yodocotz

Mentor: G. Bard Ermentrout

Purpose

- Create a model that accurately depicts the anti-inflammatory response in relation to macrophage activity and pathogen levels
- Study the effects of a time-dependent anti-inflammatory response in an immune system while simultaneously monitoring pathogen levels and macrophage counts

Review of Terms

- Pathogen: an agent that causes disease.
- Phagocytes: A cell, such as a white blood cell, that engulfs and absorbs waste material, harmful microorganisms, or other foreign bodies in the bloodstream and tissues.
- Septic Death: death caused by the presence of pathogenic organisms in the blood or tissue.
- Aseptic Death: death caused by excessive tissue damage, due to increased phagocyte levels.

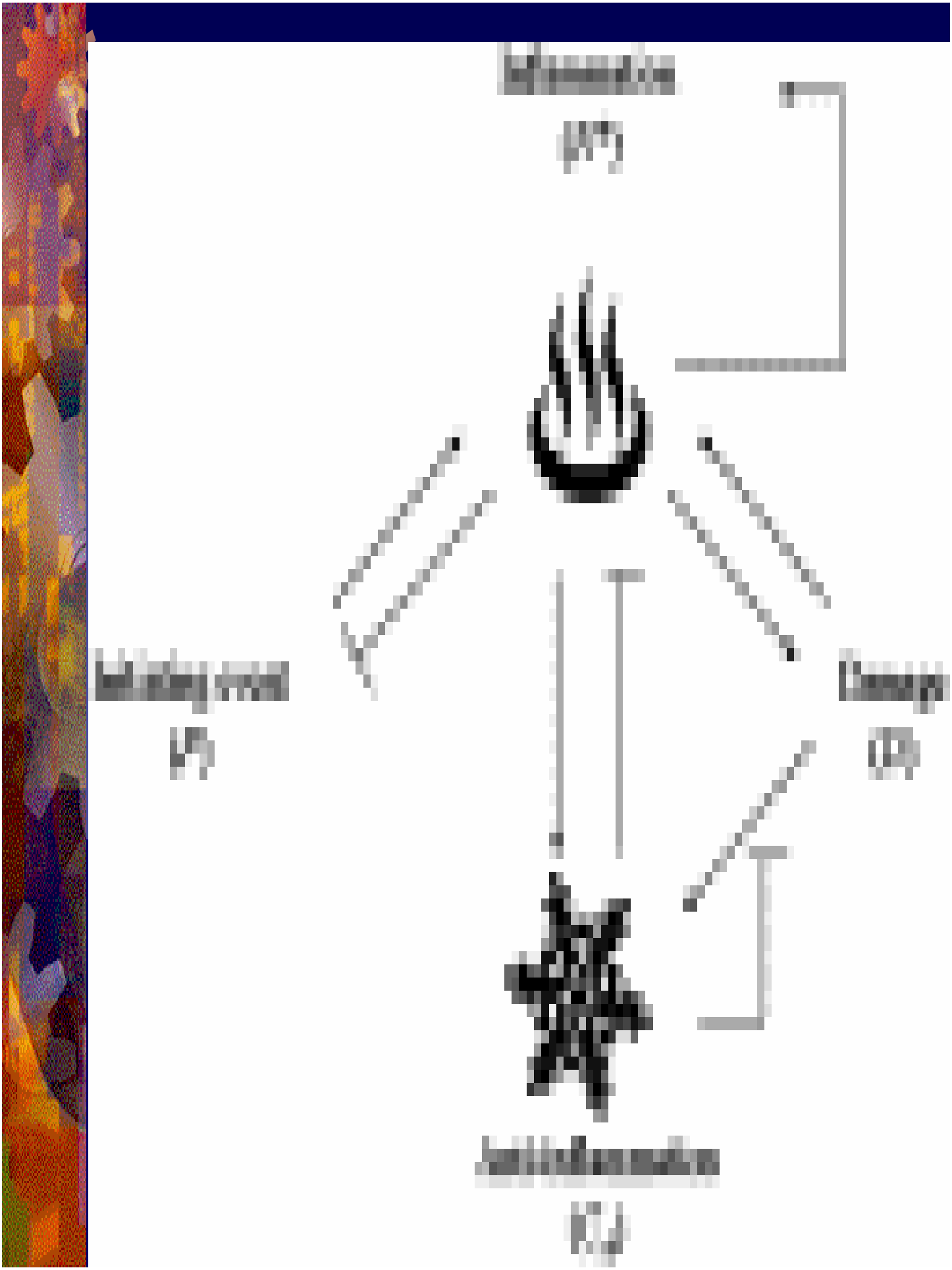
Definitions obtained from dictionary.com

Important Variables

- M: non-specific local response
- P: initiating event (pathogen levels)
- N*: inflammation (# of phagocytes)
- N_R: # of resting phagocytes
- D: collateral damage to tissue
- C_A: anti-inflammation

Interactions

- Initiating Event occurs and alerts the immune system (non-specific local response)
- Phagocytes lower pathogen levels but also cause inflammation
- Inflammation runs in a positive feedback loop
- Inflammation causes damage in tissue
- Inflammation and damage in tissue both cause anti-inflammation levels to rise



Model

- M/P Subsystem
- N*/P Subsystem
- N*/D Subsystem
- Three-Variable Subsystem
- Four-Variable Subsystem

M/P Subsystem

- The M/P subsystem models the human immune system defending its body against foreign attack.

$$\frac{dM}{dt} = s_m - \mu_m M - k_{mp} MP$$

$$\frac{dP}{dt} = -k_{mp} MP$$

$$\frac{dP}{dt} = k_{pg} P\left(1 - \frac{P}{P_\infty}\right) - \frac{k_{pm} s_m P}{\mu_m + k_{mp} MP}$$

N*/P Subsystem

- As pathogen levels increase, phagocytes are induced, and inflammation occurs as a result.
- Resting phagocytes are activated by active phagocytes.

$$\frac{dP}{dt} = k_{pg}P(1-\frac{P}{P\infty}) - \frac{k_{pm}s_mP}{\mu_m + k_{mp}P} - kN^*P$$

$$\frac{dN_R}{dt} = s_{nr} - \mu_{nr}N_R - (k_{nn}N^* + k_{np}P)N_R$$

$$\frac{dN^*}{dt} = (k_{nn}N^* + k_{np}P)N_R - \mu_nN^*$$

N*/D Subsystem

- Activated phagocytes induce collateral tissue damage.
- Damaged tissue releases pro-inflammatory cytokines, which causes further phagocyte activation.

$$\frac{dN^*}{dt} = \frac{s_{nr}(k_{nn}N^* + k_{nd}D)}{\mu_{nr} + (k_{nn}N^* + k_{nd}D)} - \mu_n N^*$$

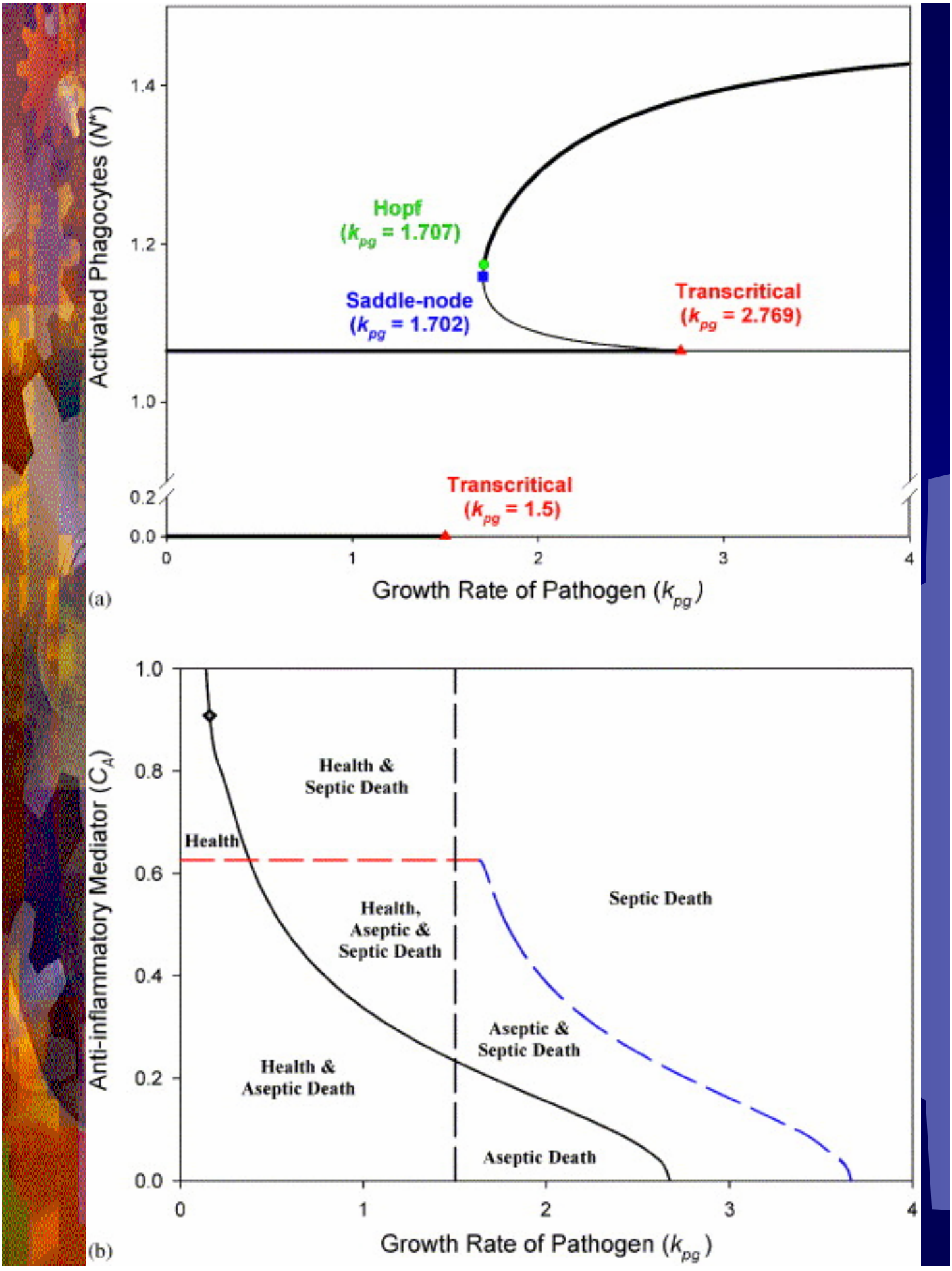
$$\frac{dD}{dt} = k_{dn}\left(\frac{N^{*6}}{x_{dn}^6 + N^{*6}}\right) - \mu_d D$$

Three-Variable Subsystem

$$\frac{dP}{dt} = k_{pg}P(1-\frac{P}{P\infty}) - \frac{k_{pm}s_m P}{\mu_m + k_{mp}P} - k_{pn}N^*P$$

$$\frac{dN^*}{dt} = \frac{s_{nr}(k_{nn}N^* + k_{np}P + k_{nd}D)}{\mu_{nr} + (k_{nn}N^* + k_{np}P + k_{nd}D)} - \mu_n N^*$$

$$\frac{dD}{dt} = k_{dn}(\frac{N^{*6}}{x_{dn}^6 + N^{*6}}) - \mu_d D$$


Activated Phagocytes (N^*)
1.4
1.2
1.0
0.2
0.0
Hopf
(k_{pg} = 1.707)
Saddle-node
(k_{pg} = 1.702)
Transcritical
(k_{pg} = 2.769)
Transcritical
(k_{pg} = 1.5)
0
1
2
3
4
Growth Rate of Pathogen (k_{pg})
(a)
Anti-inflammatory Mediator (C_A)
1.0
0.8
0.6
0.4
0.2
0.0
Health & Septic Death
Health
Health, Aseptic & Septic Death
Septic Death
Aseptic & Septic Death
Health & Aseptic Death
Aseptic Death
0
1
2
3
4
Growth Rate of Pathogen (k_{pg})
(b)

Four Variable Subsystem

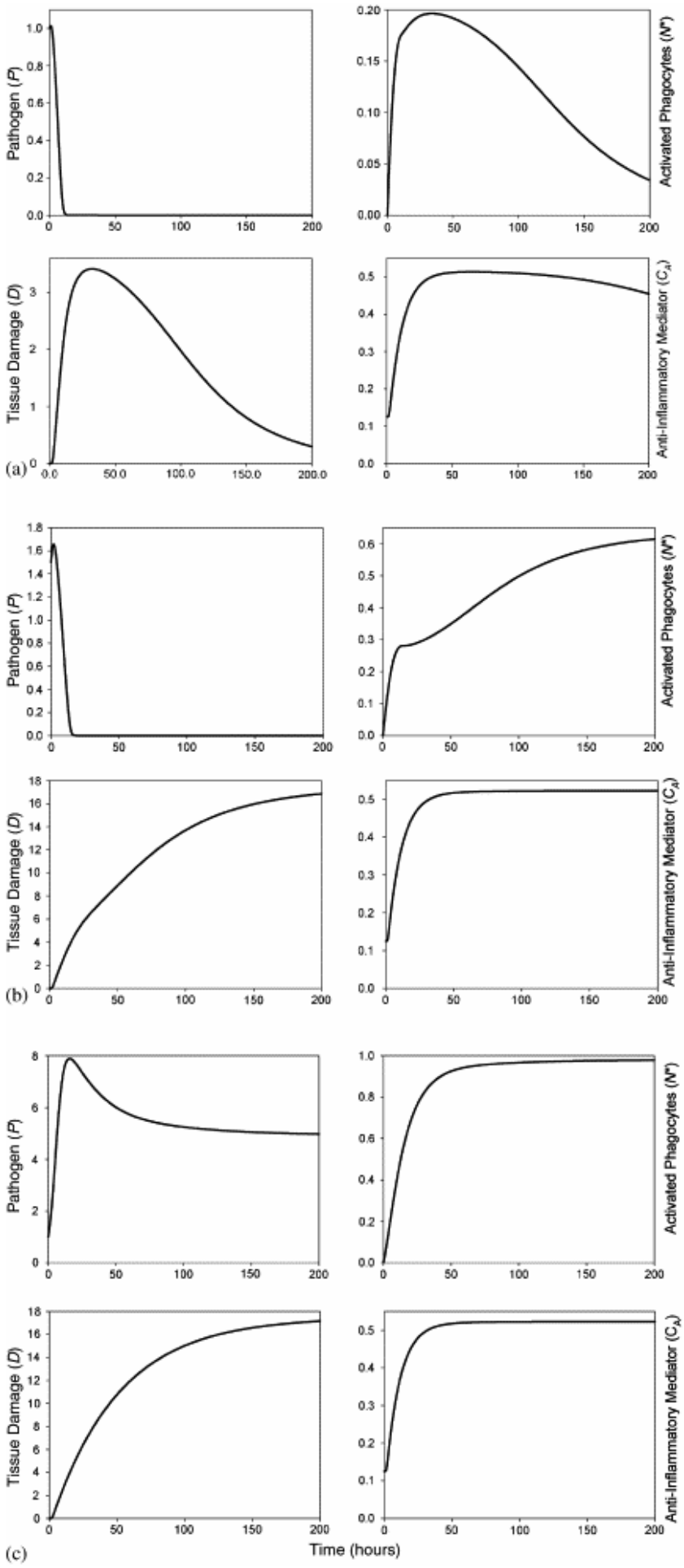
$$\frac{dP}{dt} = k_{pg} P(1 - \frac{P}{P\infty}) - \frac{k_{pm} s_m P}{\mu_m + k_{mp} P} - k_{pn} f(N^*) P$$

$$\frac{dN^*}{dt} = \frac{s_{nr} f(k_{nn} N^* + k_{np} P + k_{nd} D)}{\mu_{nr} + f(k_{nn} N^* + k_{np} P + k_{nd} D)} - \mu_n N^*$$

$$\frac{dD}{dt} = k_{dn} (\frac{f(N^*)^6}{x_{dn}^6 + f(N^*)^6}) - \mu_d D$$

$$\frac{dC_A}{dt} = s_c + \frac{k_{cn} f(N^* + k_{cnd} D)}{1 + f(N^* + k_{cnd} D)} - \mu_c C_A$$

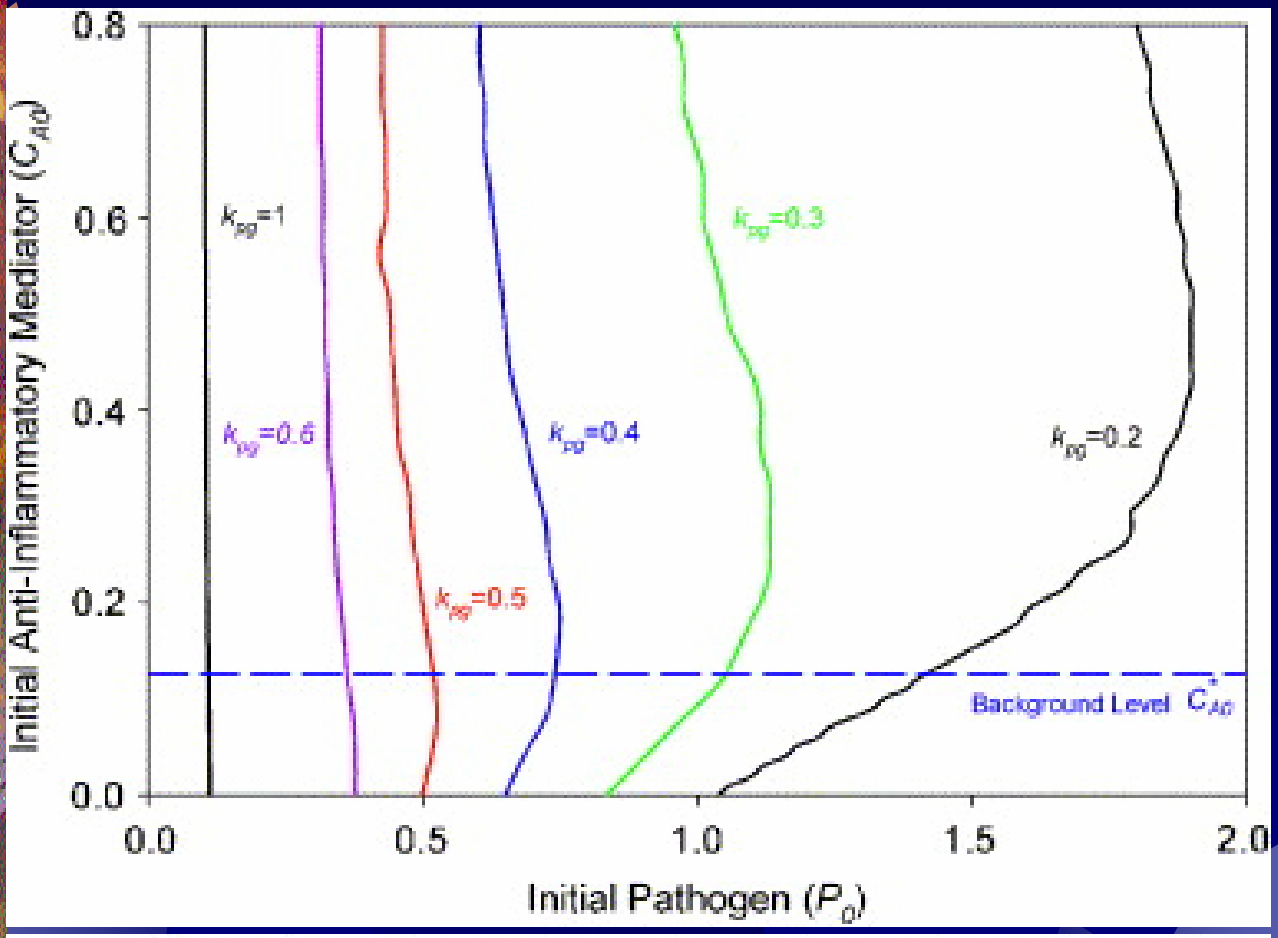
$$f(V) = \frac{V}{1 + (\frac{C_A}{c_\infty})^2}$$

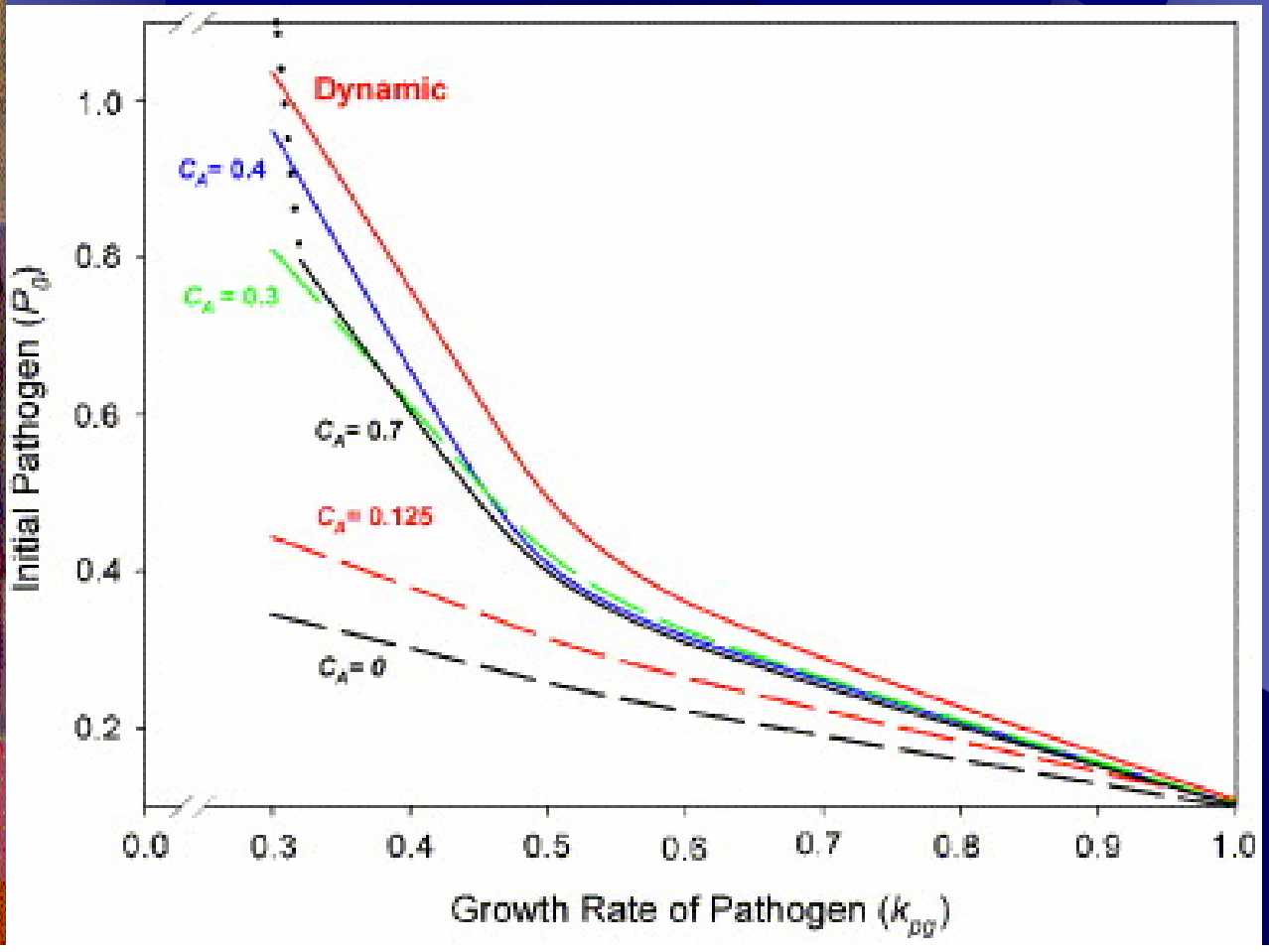


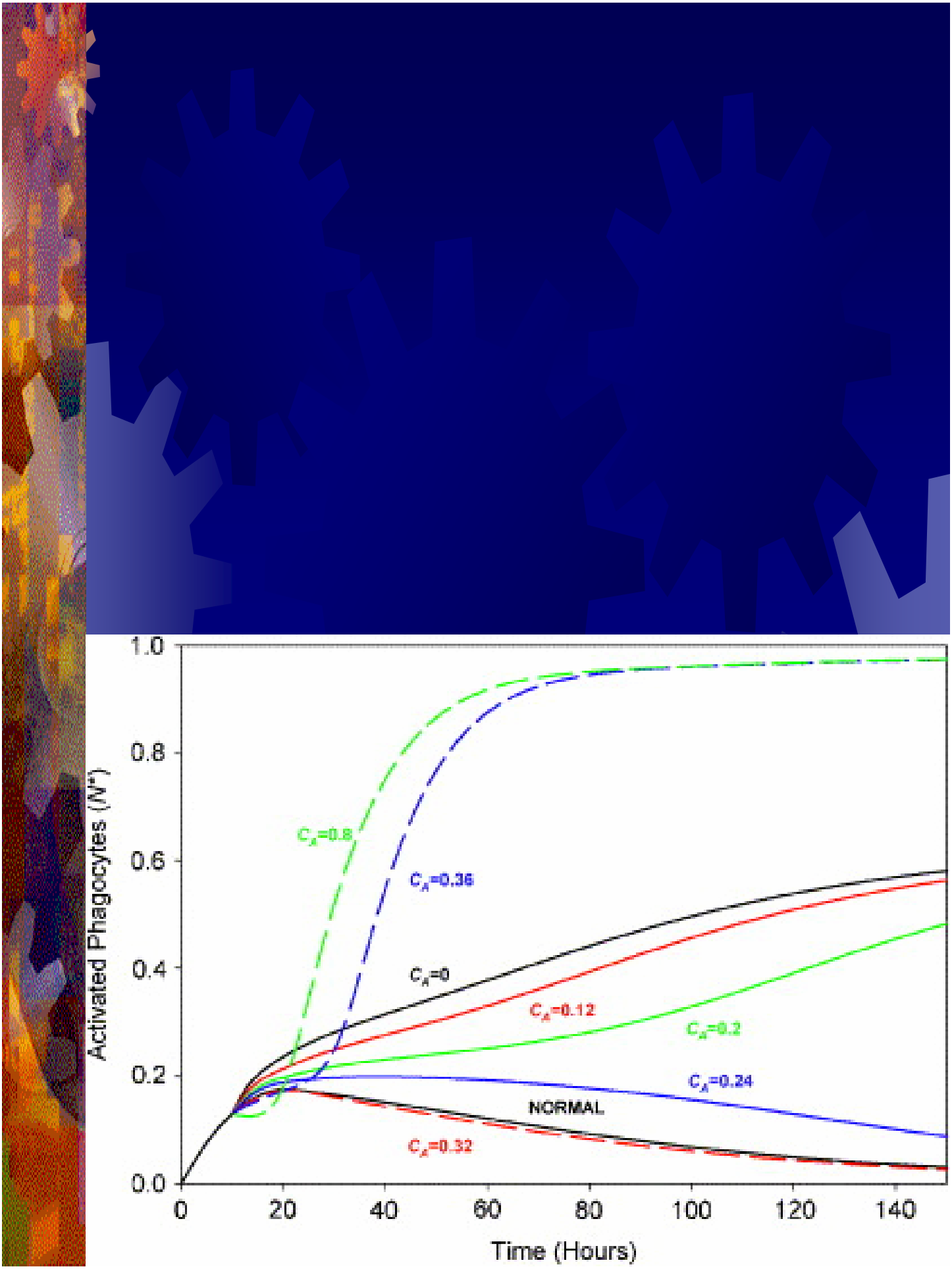
P=1, N*=0, D=0, Ca=0.125, Kpq=0.3

P=1.5, N*=0, D=0, Ca=0.125, Kpq=0.3

P=1, N*=0, D=0, Ca=0.125, Kpq=0.6


Initial Anti-Inflammatory Mediator (C_{A0})
Initial Pathogen (P_0)
k_{pg}=1
k_{pg}=0.6
k_{pg}=0.5
k_{pg}=0.4
k_{pg}=0.3
k_{pg}=0.2
Background Level C^*_{A0}
0.0
0.2
0.4
0.6
0.8
0.0
0.5
1.0
1.5
2.0


Initial Pathogen (P_0)
Growth Rate of Pathogen (k_{pg})
Dynamic
C_A= 0.4
C_A= 0.3
C_A= 0.7
C_A= 0.125
C_A= 0
0.2
0.4
0.6
1.0
0.0
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0


Activated Phagocytes (N*)
Time (Hours)
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
C_A=0.8
C_A=0.36
C_A=0
C_A=0.12
C_A=0.2
C_A=0.24
NORMAL
C_A=0.32

Conclusion

- It is advantageous to have dynamic anti-inflammatory levels.
- There is a specific range of N* and C_A for optimal health.

Limitations

- Because of our oversimplified model, the biological aspects are not as accurate as we had hoped them to be.
- It is difficult to provide quantitative measurements for functions like “pro-inflammation”, “anti-inflammation”, and “damage”.

Future Research

- How the various features of the inflammatory response interact to govern the outcome following multiple insults.
- Models that are more detailed in anti-inflammatory substances and analyze anti-inflammatory mediators as “therapeutic agents”.